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Polymorphisms of XRCC1 and risk of esophageal and gastric cardia cancer

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Abstract

Background: Linxian, a rural county in North Central China, has among the highest rates of esophageal squamous cell carcinoma and gastric cardia adenocarcinoma in the world. In a nested case-cohort study that originated from two cancer prevention trials in Linxian, we examined the relationship between these cancers and two polymorphisms in the DNA repair gene XRCC1.

Methods: We conducted a case-cohort study among individuals in the cohort who were alive and cancer free in 1991, and had blood samples for DNA extraction. Real time Taqman analyses were conducted to genotype incident cancer cases ($n = 221$, 131 esophageal and 90 gastric cardia cancer cases) that developed through May 1996, and on an age- and sex-matched reference cohort ($n = 454$). We used Cox proportional hazard models to estimate relative risks (RR) and 95% confidence intervals (95% CI).

Results: We observed no association between the variant genotype in XRCC1 Arg194Trp (codon 194 arganine to tryptophan substitution) and esophageal or gastric cardia cancer. However, carrying at least one copy of the variant allele in XRCC1 Arg399Gln (codon 399 arganine to glutamine substitution) was associated with reduced risk of gastric cardia cancer (RR: 0.60, 95% CI: 0.37–0.97) and the combined category esophageal/gastric cancer (RR: 0.67, 95% CI: 0.48–0.95). In combined polymorphisms analyses, we observed a significant reduction in risk of combined esophageal/gastric cancer among individuals that had both the XRCC1 Arg194Trp and Arg399Gln variant genotyopes (RR: 0.47, 95% CI: 0.26–0.84).

Conclusions: Our results suggest that the XRCC1 Arg399Gln variant genotype is associated with reduced risk of upper GI cancer and that individuals with both XRCC1 variant genotypes are also at significantly reduced risk of upper GI cancer in this high-risk Chinese population.

Keywords: Esophageal cancer; Gastric cardia cancer; Polymorphism; XRCC1

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1. Introduction

X-ray repair cross complementing group 1 (XRCC1) is one of the proteins involved in the repair of gaps in the restorative phase of base excision repair (BER). Other enzymes involved in BER include apurinic/apyrimidinic endonuclease (APE), polynucleotide kinase, DNA polymerase β and DNA ligase III [1,2]. BER, nucleotide excision repair, mismatch repair and double strand break repair are pathways of DNA repair involved in maintaining genomic integrity against damage caused by endogenous and exogenous mutagens. Because of the importance of maintaining cellular genomic integrity, the many enzymes involved in complex DNA repair processes are thought to be candidate cancer-susceptibility genes.

Polymorphisms in DNA repair enzyme genes, which result in amino-acid substitutions, may alter the efficiency of DNA repair and influence cancer susceptibility [3–9]. The genetic polymorphism in the XRCC1 gene at codon 194 (XRCC1 Arg194Trp), which results in an arginine to tryptophan amino acid substitution, occurs at a conserved residue in humans, hamsters, and mice, and this evolutionary conservation suggests that this site is functionally important [10,11]. The genetic polymorphism in the XRCC1 gene at codon 399 (XRCC1 Arg399Gln) results in an arginine to glutamine amino acid substitution. A report by Lunn and colleagues measured the prevalence of aflatoxin B1 adducts in placental DNA from 120 Taiwanese women and suggested that the XRCC1 Arg399Gln polymorphism may result in deficient DNA repair capacity [12]. A BCRT domain found in many proteins responsive to DNA damage with cell cycle checkpoint functions has also been identified in XRCC1 [13]. Because amino acid residues at the protein–protein interfaces of multi-protein complexes and residues involved in the active sites play a role in enzyme function, it is possible that XRCC1 polymorphisms result in altered DNA repair capacity.

Linxian, China, is a region where the rates of squamous esophageal/adenomatous gastric cardia cancer is more than 400 per 100,000 person-years [14] (approximately 100 times the rates in US whites [14]). Subjects for the current study were drawn from two randomized, placebo controlled intervention trials of nutritional supplements conducted between 1985 and 1991 in Linxian. Detailed results of these trials have been published elsewhere [15–17]. The primary objective of both Linxian trials was to test whether nutritional supplementation would reduce the rates of mortality from and incidence of esophageal and gastric cardia cancers. In the smaller of these two studies, the Dysplasia trial, a multivitamin containing selenium was randomly assigned to 3318 people with pre-existing esophageal dysplasia. At the end of the 6-year intervention, there was no statistically significant reductions esophageal or gastric cardia cancer mortality [16]. The larger trial referred to as the General Population Trial, with 29,584 participants tested four different combinations of nutrient supplements for 5.25 years. The group receiving the supplement with selenium, β-carotene, and vitamin E had a statistically significant reduction of mortality and incidence rates for esophageal/gastric cardia cancers (esophageal and gastric cardia cancers combined) by 10 and 6% compared to placebo, respectively [17]. Supplementation with selenium, β-carotene, and vitamin E had no effect on mortality and incidence rates of esophageal cancer or cardia cancer alone.

The goal of the present case-cohort study is to explore the association between the XRCC1 Arg194Trp and XRCC1 Arg399Gln polymorphisms and risk of incident esophageal and gastric cardia cancers.

2. Methods

2.1. Study population

The subjects for this study were selected from 4334 participants in the Dysplasia and General Population Nutrition Intervention Trials, who were alive and disease free at the time blood was collected in 1991 (Dysplasia = 1532 (35.3%); Genpop = 2802 (64.7%)). Individuals with >1.5 μg of DNA were considered eligible for participation in the case-cohort ($n = 4005$). We used a stratified case-cohort design [18–20] to select individuals for inclusion in this study from the cohorts. The case-cohort study design allows the use of a single reference group for study of multiple disease endpoints. All eligible incident cases of esophageal squamous cell carcinoma and gastric cardia adenocarcinoma that occurred between May, 1991 and April, 1996 were included as cases

in the study ($n = 221$). Eighteen of the 90 cardia cancer cases and 15 of the 131 esophageal cancer cases are in both the case and the referent groups. Gastric cancers were defined as cardia cancers if they were found in the most proximal 3 cm of the stomach and as non-cardia cancers if they originated outside this region. Non-cardia gastric cancers were excluded from this study due to small numbers. In addition, we selected a stratified random sample of all eligible trial participants to serve as the reference group. The six strata were defined by sex and the following three age categories: (1) 50 years old or younger, (2) older than 50 years to 60 years old, and (3) older than 60 years. The within-strata ratios of control subjects to case subjects for the incident site-specific cancers ranged from 2.3 to 5.8 for esophageal cancer, 3.7 to 7.0 for gastric cardia cancer, and 1.6 to 2.5 for the combined endpoint.

Prior to trial enrollment, at the end of trial exams (1991), and at follow-up (1996), written informed consent was obtained from each participant. Throughout the trial, human subject protection procedures were followed in accord with those prescribed by the US National Institutes of Health and the Chinese Academy of Medical Sciences.

2.2. Genotyping

Genomic DNA was extracted and genotyped for XRCC1 using real-time TaqMan analyses (Applied Biosystems, Foster City, CA) as previously described [21]. PCR primers and dual-labeled allele discrimination probes were designed using PrimerExpress™ version 1.0 (Applied Biosystems). Probes were selected that had a predicted T_m near 68 °C, with the polymorphic base near the center. Flanking PCR primers were selected based on the calculated penalty score, T_m, length, and amplimer size. Oligonucleotide sequences for the analyses were:

XRCC1 Arg194Trp:

Forward Primer: GAGGATGAGAGCGCCAA CTCT

Reverse Primer: ACGTTGTCCGAGCTCACCTG

T allele probe: CTCTTCTTCAGCTGGATCAA CAAGA

C allele probe: TCTTCTTCAGCCGGATCAA CAAG

XRCC1 Arg399Gln:

Forward Primer: GTAAGGAGTGGGTGCTGGAC TGT

Reverse Primer: GTCTGACTCCCCTCCAGATT CC

A allele probe: CTGCCCTCCCAGAGGTAAG GCCTC

G allele probe: CTGCCCTCCCGGAGGTAAGGCC

Genotyping reactions (10 μl) contained approximately 40 ng of genomic DNA, 1 × TaqMan™ Master Mix, dual-labeled probes (100 nM each), and PCR primers (900 nM each). Reactions were performed in 96-well MicroAmp® Optical reaction plates and caps (PE Biosystems). Plates were incubated at 50 °C for 2 min, 95 °C for 10 min, followed by 40 cycles of 95 °C for 15 sec and 62 °C for 1 min. Reaction data was analyzed with Sequence Detection System version 1.6.3. All laboratory personnel were blinded to case-control status of the samples and a blinded repeat genotyping of 96 of the DNA samples yielded 100% concordance for the two polymorphisms.

2.3. Statistical analysis

Significance testing for case-control differences were conducted using Wilcoxon rank-sum tests for continuous variables and χ^2-tests for categorical variables. Pearson correlation coefficients were calculated using the known sampling weights from the entire eligible cohort for each individual in the study. Covariates used in the analysis were: (1) Smoking defined as a dichotomous variable: never versus ever smoking for ≥ 6 months; (2) Drinking as a dichotomous variable: none versus any in the previous 12 months; (3) Follow-up time as days from May 1, 1991 to incident cancer or censoring at April 30, 1996; (4) Trial.

When analyzing cancers at a specific site we treated persons with cancers at other sites as censored at the time of cancer occurrence. We estimated relative risks (RR) and 95% confidence intervals (CI) using the case-cohort estimator for the Cox proportional hazards models [18–20,22]. All estimates came from models stratified on the six sex–age sampling strata. Additional stratum-specific terms for continuous age were used to adjust for variation within each age stratum. We also adjusted for tobacco smoking, alcohol drinking, and trial.

Nested models were compared using score tests. We tested the proportional hazards assumption for each main effect (genotype) with each of the three case definitions (esophagus, gastric cardia, or combined) using a time-dependent covariate (genotype*follow-up time). This test was non-significant ($P > 0.05$) in all cases. Throughout the paper, all P-values reported are 2-sided. All regression analyses were completed using the case-cohort feature of the Epicure statistical package (Hirosoft International Corp., Seattle, WA).

Because of the low allele frequencies and relative rarity of the homozygous variant genotypes, the homozygous variant and heterozygous groups were combined. Therefore, the RR reported estimate the risk of being heterozygous or homozygous variant at each site compared to being homozygous wildtype. For genotype-cancer site comparisons we tested whether the cancer RRs varied by the covariates age, sex, tobacco use, and alcohol use (i.e. interactions). We did this by comparing a model with the main effect of a covariate (e.g. sex) and a single risk parameter for the analyte to a model with the main effect term for the covariate and separate risk parameters for each sub-group (e.g. females and males) defined by the covariate. Since all models were stratified on sex and age, there was no main effect term when testing and estimating a sex interaction.

We modeled the interaction between XRCC1 Arg194Trp and XRCC1 Arg399Gln in two ways. First we stratified on one genotype and estimated the risk associated with the other variant site. For example, among individuals wildtype at XRCC1 Arg399Gln we estimated the risk of being variant at XRCC1 Arg194Trp. Second, we categorized all individuals according to the four potential combinations and simultaneously estimated the RR relative to those wildtype for both polymorphisms.

3. Results

Table 1 shows the distribution of case-cohort characteristics and the distribution of genotypes for each polymorphism by cancer status. The prevalence of the homozygous variant genotypes for both polymorphisms was low (< 10%), limiting statistical power in this stratum to test for associations.

Table 1
Case-Cohort characteristics

	Subcohort	Esophageal cancer	Gastric cardia cancer
Number	454	131	90
Mean age, yrs (SD)	58.8 (7.7)	57.4 (6.9)	60.4 (6.8)
Male, n (%)	252 (55.5)	65 (50.4)	53 (58.9)
Smoking, yes (%)[a]	177 (39.3)	48 (36.6)	43 (47.8)
Drinking, yes (%)[a]	119 (26.4)	29 (22.1)	21 (23.3)
General Population Trial, *n* (%)	289 (63.7)	54 (41.2)[b]	42 (46.7)[b]
Follow-up time, yrs (SD)	4.6 (1.0)	3.2 (1.6)	3.0 (1.7)
XRCC1 Arg194Trp[c]			
Arg/Arg, *n* (%)	217 (50.6)	68 (54.4)	44 (51.2)
Arg/Trp, *n* (%)	194 (45.2)	48 (38.4)	36 (41.9)
Trp/Trp, *n* (%)	18 (4.2)	9 (7.2)	6 (7.0)
Arg/Trp + Trp/Trp, *n* (%)	212 (49.4)	57 (45.6)	42 (48.9)
XRCC1 Arg399Gln[c]			
Arg/Arg, *n* (%)	192 (45.9)	66 (52.4)	49 (57.0)
Arg/Gln, *n* (%)	193 (46.2)	48 (38.1)	34 (39.5)
Gln/Gln, *n* (%)	33 (7.9)	12 (9.5)	3 (3.5)
Arg/Gln + Gln/Gln, *n* (%)	226 (54.1)	60 (47.6)	37 (43.0)

[a] Smoking as a dichotomous variable never versus ever and drinking as a dichotomous variable none versus any in the previous 12 months.
[b] Differed from non-case control subjects, χ^2-test, $P < 0.05$.
[c] Correlation coefficient and P-value for association between genotypes; $r = 0.34$, $P < 0.0001$.

Table 2
Relative risks and 95% CI for the associations between genotype and cancer

		Combined cancer		Esophageal Cancer		Gastric Cardia cancer	
		RR (95%CI)	P^a	RR (95%CI)	P^a	RR (95%CI)	P^a
Arg194Trp	Arg/Arg	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
	Arg/Trp + Trp/Trp[b]	0.94 (0.67–1.32)	0.53	0.89 (0.59–1.35)	0.54	1.02 (0.64–1.63)	0.40
Arg399Gln	Arg/Arg	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
	Arg/Gln + Gln/Gln[b]	0.67 (0.48–0.95)	0.012	0.73 (0.48–1.11)	0.08	0.60 (0.37–0.97)	0.022

[a] *P*-values are from score tests for the addition of the main effect term to the base model.
[b] Relative risks calculated using a Cox model stratified on sex and age categories with additional adjustment for age, smoking, drinking, and trial.

Table 2 gives the RR and 95% CI for the polymorphisms and cancer with the heterozygous and homozygous-variant categories combined to increase statistical power. There was no association between the XRCC1 Arg194Trp variant genotype and either esophageal or cardia cancer. However, individuals carrying one or two copies of the XRCC1 Arg399Gln variant genotype were at significantly reduced risk of gastric cardia cancer (RR: 0.60, 95% CI: 0.37–0.97) and combined esophageal/gastric cancer (RR: 0.67, 95% CI: 0.48–0.95) after adjusting for age, smoking, alcohol drinking, sex, and trial. Adjustment for intervention group in the trials did not alter the risk estimates (data not shown).

Table 3 shows combined polymorphisms analyses examining the interaction between the two XRCC1

Table 3
XRCC1 Arg194Trp and XRCC Arg399Gln interaction relative risks

Strata	Genotype estimated	Combined esophageal/gastric cardia cancer		Esophageal Cancer		Gastric Cardia cancer	
		RR (95%CI)	P_{1df}[a]	RR (95%CI)	P_{1df}[a]	RR (95%CI)	P_{1df}[a]
Arg399Gln-wt[b]	Arg194Trp-vt[b]	1.13 (0.77–1.68)	0.017	1.03 (0.63–1.67)	0.071	1.30 (0.77–2.19)	0.037
Arg399Gln-vt[b]	Arg194Trp-vt[b]	0.60 (0.36–0.99)		0.61 (0.33–1.12)		0.59 (0.28–1.24)	
Arg194Trp-wt[b]	Arg399Gln-vt[b]	0.72 (0.49–1.07)	0.005	0.71 (0.44–1.15)	0.025	0.76 (0.44–1.29)	0.034
Arg194Trp-vt[b]	Arg399Gln-vt[b]	0.50 (0.30–0.84)		0.52 (0.28–0.97)		0.47 (0.23–1.00)	
Combined estimates		RR (95%CI)	P_{3df}[c]	RR (95%CI)	P_{3df}[c]	RR (95%CI)	P_{3df}[c]
	Arg194Trp-wt[b]; Arg399Gln-wt[b]	1.00 (ref)	0.030	1.00 (ref)	0.080	1.00 (ref)	0.140
	Arg194Trp-wt[b]; Arg399Gln-vt[b]	0.67 (0.41–1.10)		0.60 (0.34–1.09)		0.83 (0.41–1.65)	
	Arg194Trp-vt[b]; Arg399Gln-wt[b]	0.89 (0.54–1.45)		0.76 (0.42–1.37)		1.15 (0.58–2.26)	
	Arg194Trp-vt[b]; Arg399Gln-vt[b]	0.47 (0.26–0.84)		0.45 (0.22–0.90)		0.52 (0.22–1.23)	

Relative risks and 95%CI calculated using a Cox model stratified on sex and age with additional adjustment for age, smoking, drinking, sex, and trial.
[a] This 1 degree-of-freedom *P*-value is the test for interaction and comes from the score test comparing the model with a single variable for genotype compared to a model with stratum-specific variables for genotype.
[b] Arg194Trp-wt: Arg/Arg genotype, Arg194Trp-vt: Arg/Trp or Trp/Trp, Arg399Gln-wt: Arg/Arg genotype, Arg399Gln-vt: Arg/Gln or Gln/Gln.
[c] This 3 degree-of-freedom *P*-value is the test of association for the combined genotype variable.

polymorphisms and upper GI cancer. Assessment of intra-gene interactions for the two XRCC1 polymorphisms revealed a number of statistically significant interactions (see Table 3). Among individuals with at least one XRCC1 Arg399Gln variant allele, there was a significant association between the variant-XRCC1 Arg194Trp genotype and combined cancer risk (RR: 0.60, 95% CI: 0.36–0.99), compared to individuals with the wildtype-XRCC1 Arg194Trp genotype. Similarly, among individuals with at least one variant-XRCC1 Arg194Trp allele, there was a significant association between the variant-XRCC1 Arg399Gln genotype and combined cancer risk (RR: 0.50, 95% CI: 0.30–0.84) and also esophageal (RR: 0.52, 95% CI: 0.28–0.97) and cardia (RR: 0.47, 95% CI: 0.23–1.00) cancer risk, compared to individuals with the wildtype-XRCC1 Arg399Gln genotype. In Table 3, we also show the joint risk estimates when individuals were classified according to the four categories generated from the two XRCC1 polymorphisms. Individual with both the XRCC1 Arg194Trp and Arg399Gln-variant genotypes were at significantly reduced risk of combined cancer (RR: 0.47, 95% CI: 0.26–0.84) and esophageal cancer (RR: 0.45, 95% CI: 0.22–0.90) compared to individuals that were wildtype for both polymorphisms.

4. Discussion

Esophageal squamous cell carcinoma is one of the most prevalent cancers in China and it has been postulated that carcinogens such as polycyclic aromatic hydrocarbons (PAHs), nutritional deficiencies and other environmental factors cause this disease [23]. In addition to esophageal cancer, the incidence of gastric cardia cancer is also quite high in China and a number of environmental factors including smoking, alcohol consumption and dietary practices have been postulated to influence risk of this disease [24].

DNA repair systems act to maintain genomic integrity in the face of environmental insults, cumulative effects of age and DNA replication errors. XRCC1 is thought to play a role in the multi-step BER pathway where ‘non-bulky’ base adducts produced by methylation, oxidation, reduction, or fragmentation of bases by ionizing radiation or oxidative damage are removed [25]. XRCC1 appears to form complexes with DNA ligase III via a BRCT domain in its carboxyl terminus, with DNA polymerase β in its amino terminus and with poly(ADP-ribose) polymerase to repair gaps left during BER. Lack of XRCC1 activity in mice is an embryo-lethal condition; thus the human XRCC1 polymorphisms most probably do not cause complete loss of protein function. The XRCC1 Arg194Trp amino acid substitution resides in the linker region separating the DNA polymerase β domain from the poly(ADP-ribose) polymerase-interacting domain. The XRCC1 Arg399Gln change occurs in the carboxyl terminal side of the poly(ADP-ribose) polymerase-interacting domain and within an identified BRCT domain [26]. Amino acid substitutions in the BRCT domain and in the DNA polymerase β interacting domain in the hamster have been reported to disrupt the functionality of XRCC1 [27].

Currently there are two reports that have examined the association between the XRCC1 polymorphisms and esophageal cancer risk [28,29]; and one [30] that reported the influence of XRCC1 polymorphisms on cardia cancer risk. Xing et al., [28] and Lee et al., [29] reported that the XRCC1 Arg399Gln variant genotype appeared to be associated with reduced risk of esophageal squamous cell carcinoma but, neither risk estimate was statistically significant. Shen et al. [30] reported that the XRCC1 Arg194Trp variant genotype was associated with a statistically significant reduction in cardia cancer risk with an odds ratio of 0.5 among individuals with at least one variant allele compared to those that were wildtype (the most prevalent genotype).

Our study is a case-cohort study nested in two randomized, placebo controlled intervention trial cohorts. In the trials nutritional supplements were tested for chemoprevention of squamous esophageal and gastic cardia cancer [15–17]. In the current case-cohort study, intervention group in the trials was not associated with reduced risk of either esophageal or cardia cancer. Our findings suggest that the XRCC1 Arg399Gln variant genotype is associated with reduced risk of cardia cancer (RR: 0.60, 95%CI: 0.37–0.97). Individuals with one or two variant alleles were at 40% reduced risk of cardia cancer compared to those with the homozygous wild-type genotype after adjusting for age, sex, smoking, drinking, and trial. The risk estimate for the XRCC1 Arg399Gln polymorphism and esophageal cancer

(RR: 0.73, 95% CI: 0.48–1.11) while nonsignificant, was also protective, consistent with the other two previously published reports. The XRCC1 Arg194Trp polymorphism was not associated with either esophageal or cardia cancer risk. Combined polymorphisms analyses revealed that individuals with both XRCC1 Arg194Trp and Arg399Gln variants were at significantly reduced risk of both esophageal (RR: 0.52) and cardia cancer (RR: 0.47).

The greatest short coming of our study is its rather small sample size. The generalizability of these results may also be somewhat restricted because the study was conducted among a rather unique group of individuals at very high risk of upper GI cancer. Our study has several strengths. It was conducted in a well-defined cohort of subjects of Chinese ethnicity, with cases that arose prospectively and were carefully documented and reviewed. The case-cohort design enabled us to avoid biases related to control selection and case survival, as well as to estimate gene frequencies for an entire population from just a sample. The ethnic homogeneity avoids the problem of confounding due to population admixture. The collection of covariate data (e.g. smoking and alcohol) before case diagnosis minimized the potential for recall bias for measures of environmental exposures.

In conclusion, we observed a significant protective association between the variant XRCC1 Arg399Gln genotype and combined esophageal/gastric cardia cancer. This association is consistent with that of other studies on XRCC1 polymorphisms and upper GI cancer. Our results also suggest that individuals that were variant for both XRCC1 polymorphisms were at significantly reduced risk for combined esophageal/gastric cardia cancer.

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